FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV. 1094)	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	K0448/7003
	09/673341 U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP99/01868	08 April 1999 (08.04.99)	17 April 1998 (17.04.98)

TITLE OF INVENTION
ADHESIVE PREPARATIONS

APPLICANT(S) FOR DO/EO/US
KURITA, Hisakazu, TATEISHI, Tetsuro, CHONO, Hideharu, HIGO, Naruhito

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)) with verification of translation.

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371§(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(C)(5)).

Items 11. To 16. Below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 with references.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification (submitted as a first Preliminary Amendment).

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:
    Copy of PCT Written Opinion with a sworn English translation
    Copy of Response to Written Opinion with a sworn English translation
    Copy of PCT International Preliminary Examination Report w/a sworn English translation
    Copy of PCT Published Application w/international Search Report and English translation of Search Report
    Copy of PCT/IB/301, 304, 306, 308, and 332

Express Mail Label No. EL682257191US Mailed October 13, 2000

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION	ATTORNEY'S DOCKET NUMBER
09/673541	PCT/JP99/01868	K0448/7003

17. X The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):	CALCULATIONS	PTO USE ONLY
Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).. $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $1000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 X 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	12-20 =	0	X $18.00	$0.00	
Independent Claims	1 - 3 =	0	X $78.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$270.00	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$860.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$860.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate coversheet (37 CFR 3.28, 3.31). $40.00 per property +				$0.00	
TOTAL FEES ENCLOSED =				$860.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ 860.00 to cover the above fees is enclosed.

b. Please charge by Deposit Account No. _____ In the amount of $_____ To cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23/2825. A duplicate of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SIGNATURE

SEND ALL CORRESPONDENCE TO

John R. Van Amsterdam
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210

John R. Van Amsterdam
NAME

40,212
REGISTRATION NO

ATTORNEY'S DOCKET NO. **K0448/7003**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KURITA et al.
Int'l Application No.:	PCT/JP99/01868
Int'l Filing Date :	April 8, 1999
U.S. Serial No:	Unknown
Filed:	Herewith
For:	ADHESIVE PREPARATIONS

Box PCT
COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the application as follows, prior to calculation of the fees.

In the Claims

Please amend the claims as follows:

3. (amended) The adhesive preparation according to claim 1 [or 2] comprising the organic acid salt of 0.01-15% by weight.

4. (amended) The adhesive preparation according to claim 1 [or 2] comprising the base drug salt of 0.1-20% by weight.

5. (amended) The adhesive preparation according to [any one of] claim[s] 1 [to 3], characterized in that the organic acid salt is an acetic acid salt.

Please add the following new claims:

7. The adhesive preparation according to claim 2 comprising the organic acid salt of 0.01-15% by weight.

8. The adhesive preparation according to claim 2 comprising the base drug salt of 0.1-20% by weight.

9. The adhesive preparation according to claim 2, characterized in that the organic acid salt is an acetic acid salt.

10. The adhesive preparation according to claim 9, characterized in that the organic acid salt is sodium acetate.

11. The adhesive preparation according to claim 3, characterized in that the organic acid salt is an acetic acid salt.

12. The adhesive preparation according to claim 11, characterized in that the organic acid salt is sodium acetate.

Remarks

Please enter this amendment prior to calculation of the fees. Original PCT claims 3, 4 and 5 were amended to remove multiple dependencies, and claims 7-12 were added accordingly to claim the subject matter of the original claims. New claim 7 corresponds to original claim 3. New claim 8 corresponds to original claim 4. New claims 9 and 11 correspond to original claim 5. New claims 10 and 12 correspond to original claim 6. No new matter has been added.

Respectfully submitted,

John R. Van Amsterdam, Reg. No. 40,212
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210
Tel.: (617) 720-3500

Docket No.: K0448/7003
Date: October 13, 2000
X10/17/00

Specification

Title of the Invention: Adhesive preparations

TECHNICAL FIELD

The invention relates to a percutaneous absorption preparation which contains a salt of a base drug and is excellent in skin permeability of the drug.

BACKGROUND ART

As administration methods for drugs, various methods such as oral administration, rectal administration, intracutaneous administration and intravenous administration are known, and among them oral administration is widely been adopted. However, in case of oral administration, there are drawbacks that a drug is susceptible to the first-pass effect in the liver after absorption of the drug and an unnecessarily high blood concentration is recognized for a while after the administration. Also, in oral administration many side effects such as gastrointestinal tract disorder, vomiting feeling and loss of appetite have been reported. Further, in recent aged society patients with reduced swallowing power increase, and preparations easy for administration clinically are desired.

Therefore, by dissolving these drawbacks of oral administration with the aim of percutaneous preparations for patients to take more easily with safety and persistence, development of such percutaneous administration preparations has actively been carried out, and the products are commercially

available.

However, percutaneous absorbance of drugs in said percutaneous administration preparations is still insufficient in many cases, and the development of percutaneous administration preparations is difficult due to low percutaneous absorbance of most drugs, so it can hardly be said that the objects have sufficiently been attained. Namely, since normal skin has barrier function to prevent penetration of foreign substances, sufficient percutaneous absorption of a compounded pharmaceutically active ingredient is hardly attained in many cases.

Therefore, devices to increase percutaneous absorbance of a drug through a stratum corneum of skin has been needed, and compounding so-called percutaneous absorption promotors to a base has generally been tried. For example, as an absorption promotor combined with a lower alkyl amide, dimethylacetamide and ethyl alcohol, isopropyl alcohol, isopropyl palmitate or the like (US, 3,472,931, A), combining 2-pyrrolidone and an appropriate oil, and a straight chain fatty acid and alcohol ester ((US, 4,017,641, A), and combining lower alcohol and C_7-C_{20} alcohol, C_5-C_{30} fatty acid hydrocarbon, alcohol ester of C_{19}-C_{26} fatty acid carboxylic acid, C_{10}-C_{24} mono- or di-ether, C_{11}-C_{15} ketone and water (JP, 61-249934, A) and the like have been proposed. However, it can hardly be said that these conventional absorption promotors and absorption promoting compositions are yet sufficiently safe for skin.

Further, as a percutaneous absorption preparation, methods of combining a drug and an organic acid have been reported. For example, a tape preparation combining betamethazone valerate and an organic acid to a natural rubber type adhesive (JP, 56-61312, A), a tape preparation combining a non-steroidal anti-inflammatory agent and an organic acid to an acrylic type adhesive agent (JP, 62-126119, A (US 4,740,374, A)), and a pap type preparation combining methyl salicylate as a pharmaceutically effective ingredient, an emulsifier, an organic acid, a plasticizer, a tackifying resin and water to a stylene-isoprene-stylene block copolymer (JP, 63-159315, A) and the like have already been proposed. However, the aim of using these organic acids in the above publications is to improve stability and solubility, and was a pH-adjusting agent, and because these drugs are acidic or neutral, they are not the preparations in which skin permeability of a physiologically active substance is improved via an ion-pair formation constructed by an organic acid of the present invention.

Further, a method to improve skin permeability of a basic physiologically active substance has been tried. For example, a tape preparation combining citric acid and isoproterenol hydrochloride to an acrylic type adhesive (JP, 63-79820, A), a tape preparation combining an organic acid and vinpocetine to an acrylic type adhesive (JP, 5-25039, A) and the like have been reported, though these have a problem of irritancy at the time of dissection, and that the released amount of the drugs do not

give a sufficient effect for therapy.

The invention was made to dissolve the problems of the prior art described above, and makes it an object to provide a matrix type adhesive preparation. In WO, 96/16642, A, technology of an adhesive preparation in which an organic acid salt is contained in a salt type base drug is disclosed, though the effect of the particle size of the contained organic salt is not demonstrated.

DISCLOSURE OF THE INVENTION

During extensive researches to solve these problems the inventors found out that comprising an organic acid salt of a particular particle size in adhesive preparations containing a base drug as a salt form improves solubility of the drug to skin via an ion-pair formation, and that it significantly improves skin permeability of the drug by enhancing partition coefficient to skin, and thus accomplished the invention. Specifically, in case of the mean diameter of a base drug and an organic acid salt contained was 100μm or less (this particle size indicates volume average particle size when measured by the use of a particle fineness analyzer) the effect was observed. Particularly, it was revealed that in a fat-soluble base, though the solubility of a drug and an organic acid salt was so bad they remain as powder in the preparation, percutaneous absorbance of the drug was greatly affected by the size of the particle diameter of the organic acid salt. In particular, as an organic acid salt, the effect of sodium acetate is high, and in this case the average particle size of 0.1-10μm shows extremely excellent percutaneous

drug-absorbance promoting effect.

Accordingly, the invention relates to an adhesive preparation comprising a base drug salt, and an organic acid salt in which the mean diameter is 0.1-100μm.

The invention also relates to the above adhesive preparation wherein the mean diameter of the organic acid salt is 0.1-10μm.

Further, the invention relates to the above adhesive preparation comprising the organic acid salt of 0.01-15% by weight.

The invention also relates to the above adhesive preparation comprising the base drug of 0. 1-20% by weight.

Furthermore, the invention relates to the above adhesive preparation characterized in that the organic acid is acetic acid.

And the invention relates to the above adhesive preparation characterized in that the organic acid is sodium acetate.

Further, adhesive preparations of the invention provide excellent skin permeability, skin irritancy and content stability of a drug and physical stability of a base.

The adhesive preparations of the invention are also preferably matrix type preparations.

Brief Description of Drawing

Fig. 1

Graph showing the results of skin permeability of Examples 1-3 and Comparative example 1.

Fig. 2

Graph showing the results of skin permeability of Examples 6-8 and Comparative examples 4-5.

Fig. 3

Graph showing the results of skin permeability of Examples 11-13 and Comparative examples 8-9.

In any drug, powders with a smaller particle size gave more excellent skin permeability to the drug.

Embodiment of the Invention

As the embodiment of the invention, the composition and the form in the adhesive layer of the adhesive preparations related to the invention is explained.

Illustrative of the organic acid salts used in the adhesive layer of the adhesive preparations according to the invention are respective water-soluble inorganic salts of aliphatic (mono, di, tri)carboxylic acids (e.g., acetic acid, propionic acid, isobutylic acid, caproic acid, lactic acid, maleic acid, pyruvic acid, oxalic acid, succinic acid, tartaric acid, etc.) , aromatic carboxylic acids (e.g., phthalic acid, salicylic acid, benzoic acid, acetyl salicylic acid, etc.), alkyl sulfonic acids (e.g., ethane sulfonic acid, propyl sulfonic acid, butane sulfonic acid, polyoxyetylene alkyl ether sulfonic acid, etc.), alkyl sulfonic acids (e.g., N-2-hydroxyethyl piperidine-N'-2-ethane sulfonic acid (hereafter abbreviated as HEPES) etc.) and cholic acid derivatives (e.g., dehydro cholic acid, etc.), and in particular sodium acetate is preferable. Further, these organic acid salts may be anhydrous or hydrated, though in case used in a hydrophobic

adhesive layer, an anhydride is preferred.

Considering a sufficient permeable amount and irritancy to the skin for an adhesive preparation, these organic salts can be blended in an amount of preferably 0.01-15% by weight, more preferably 0.1-10% by weight, and most preferably 0.1-5% by weight based on the total weight of the composition in the adhesive preparation.

Also, in the case of a commercially available powder in which the average particle size of an organic acid salt is not less than about 100μm (in the case of sodium acetate, generally the average particle size of commercially available one is not less than about 500μm), it is ground in a preparation step to not more than 100μm to obtain an excellent percutaneous drug absorbance, and the average particle size is made preferably 0.1-100μm, more preferably 0.1-50μm, and most preferably 0.1-10μm. Namely, it is considered that an ion-pair formation is more sufficiently promoted as the particle size of powders becomes smaller. As a method to grind an organic acid salt, powders which are dry ground beforehand may be used, or not yet ground one is added to a solution containing other base ingredients and may be wet ground under stirring. For example, as a grinder mill of dry process, a supersonic jet grinder mill, Jet Mill, (manufactured by Nippon Pneumatic MFG Co., Ltd.) and the like, or as a grinder mill of wet process, an ultra-micro grinder mill, Micros, (manufactured by Nara Machinery Co., Ltd.) and the like can be used.

Further, as a drug used in the adhesive layer of the adhesive

preparations of the invention, an inorganic salt forming an ion-pair with an organic acid or its salt, or any base drug salt formed by an organic acid is not limited particularly by their types; examples include hypnotic-sedative agents (fluazepam hydrochloride, rilmazafone hydrochloride, etc.), anti-inflammatory agents (butorphanol tartarate, persoxal citrate, etc.), excitation-analeptic agents (methanephetamine hydrochloride, methylphenidate hydrochloride, etc.), psychotropic agents (chlorpromazine hydrochloride, imipramine hydrochloride, etc.), local anesthetic agents (lidocain hydrochloride, procaine hydrochloride), agents for urinary organs (oxybutynin hydrochloride, etc.), skeletalmuscle relaxants (tizanidine hydrochloride, eperisone hydrochloride, pridinol mesilate, etc.), autonomic agents (carpronium chloride, neostigmine bromide, etc.), anti-Parkinson's disease agents (trihexyphenidyl hydrochloride, amantadine hydrochloride, etc.), antihistaminic agents (clemastine fumarate, diphenhydramine tannate, etc.), bronchodilator agents (tulobuterol hydrochloride, procaterol hydrochloride, etc.), cardiotonic agents (isoprenaline hydrochloride, dopamine hydrochloride, etc.), coronary dilators (diltiazem hydrochloride, verapamil hydrochloride, etc.), peripheral vasodilators (nicametate citrate, tolazoline hydrochloride, etc.), cardiovascular agents (flunarizine hydrochloride, nicardipine hydrochloride, etc.), antiarrhythmic agents (propranolol hydrochloride, alprenolol hydrochloride, etc.), antiallergic agents (ketotifen fumarate,

azelastine hydrochloride, etc.), anti-dizziness agents (betahistine mesilate, difenidol hydrochloride, etc.), serotonin receptor antagonistic antiemetics, narcotic analgesic agents (morphine sulfate, fentanyl citrate, etc.).

Further, these drugs may be used alone or in combination of two or more of them, and any form of drug, an inorganic salt or an organic salt, are naturally included. Also, considering a sufficient permeable amount as adhesive preparations and irritancy to the skin such as rubor, drugs can be blended in an amount preferably of 0.01-15% by weight, and more preferably 0.1-20% by weight based on the total weight of the composition in the adhesive layer.

Any absorption promotor may be contained in the adhesive layer of the adhesive preparations of the invention, and as an absorption promotor, any compound in which absorption promoting effect is shown may be used. Examples include C_6-C_{20} fatty acids, fatty alcohols, fatty acid esters or ethers, aromatic organic acids, aromatic alcohols, aromatic fatty acid esters or ethers (these may be saturated or unsaturated, and cyclic, straight or branched), furthermore lactic acid esters, acetic acid esters, monoterpene compounds, sesquiterpene compounds, Azone, Azone derivatives, glycerol fatty acid esters, sorbitan fatty acid esters (Span type), polysorbates (Tween type), polyethylene glycol fatty acid esters, polyoxyethylene hardened castor oils (HCO type), sucrose fatty acid esters and the like.

Specifically, caprylic acid, capric acid, lauric acid,

myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, lauryl alcohol, myristyl alcohol, oleyl alcohol, cetyl alcohol, methyl laurate, isopropyl myristate, myristyl myristate, octyldecyl myristate, cetyl palmitate, salicylic acid, methyl salicylate, glycol salicylate, cinnamic acid, methyl cinnamate, cresol, cetyl lactate, ethyl acetate, propyl acetate, geraniol, thymol, eugenol, terpineol, 1-menthol, borneol, d-limonene, isoeugenol, isoborneol, nerol, dl-camphor, glycerol monolaurate, glycerol monooleate, sorbitan monolaurate, sucrose monolaurate, polysorbate 20, propylene glycol, polyethylene glycol monolaurate, polyethylene glycol monostearate, HCO-60, and 1-[2-(decylthio)ethyl]azacyclopentan-2-one (hereafter abbreviated as pyrothiodecane) are preferred, and lauryl alcohol, 1-menthol, propylene glycol and pyrothiodecane are particularly preferred.

Considering a sufficient permeable amount as adhesive preparations and irritancy to the skin such as rubor and edema, such absorption promotors can be blended in an amount preferably of 0.01-20% by weight, more preferably 0.05-10% by weight and most preferably 0.1-5% by weight based on the total weight of the composition in the adhesive preparations.

As a fat soluble hydrophobic polymer used in the adhesive layer of the adhesive preparations of the invention, examples include styrene-isoprene-styrene block copolymer (hereinafter abbreviated as SIS), isoprene rubber, polyisobutylene (hereinafter abbreviated as PIB), styrene-butadiene-styrene

block copolymer (hereinafter abbreviated as SBS), styrene-butadiene rubber (hereinafter abbreviated as SBR), acrylic type polymer (copolymer of at least two types from 2-ethylhexyl acrylate, vinyl acetate, methacrylate, methoxyethyl acrylate and acrylic acid). In particular, SIS, PIB or blends thereof, and acrylic type polymer are preferred.

Considering formation of the adhesive layer and sufficient permeability, the blended amount of such hydrophobic polymers based on the total weight of the composition in the adhesive layer can be 10-60% by weight, preferably 15-50% by weight, more preferably 18-40% by weight in SIS, PIB or the like. Similarly, it can be 10-98% by weight, preferably 20-98% by weight, more preferably 30-98% by weight in acrylic type polymer.

As a tackifying resin used in the adhesive layer of the adhesive preparations of the invention, examples include rosin derivatives (e.g,. rosin, glycerol esters of rosin, hydorogenated rosin, glycerol esters of hydorogenated rosin, pentaerythritol esters of rosin, etc.), alicyclic saturated hydrocarbon resins, aliphatic hydrocarbon resins, terpene resins, maleic acid resins and the like. In particular, glycerol esters of hydorogenated rosin, alicyclic saturated hydrocarbon resins, aliphatic hydrocarbon resins and terpene resins are preferred.

Considering sufficient adhesive strength as the adhesive preparations and irritancy to the skin at the time of dissection, the compounded amount of such tackifying resins based on the total weight of the composition in the adhesive layer can be 10-70%

by weight, preferably 15-60% by weight, and more preferably 20-50%.

As a plasticizer used in the adhesive layer of the adhesive preparations of the invention, examples include petroleum oils (e.g., paraffin type process oil, naphthalene type process oil, aromatic type process oil, etc.), squalene, vegetable oils (olive oil, camellia oil, castor oil, tall oil, peanut oil), dibasic acid esters (e.g., dibutyl phthalate, dioctyl phthalate, etc.), liquid rubber (e.g., polybutene, liquid isoprene rubber), diethylene glycol, polyethylene glycol, glycol salicylate, propylene glycol, dipropylene glycol, crotamiton and the like. In particular, liquid paraffin, liquid polybutene, glycol salicylate and crotamiton are preferred.

Considering sufficient permeability and the maintenance of sufficient agglutinative strength as adhesive preparations, the blended amount of such a tackifying resin based on the total weight of the composition in the adhesive layer can be 10-70% by weight, preferably 15-60% by weight, and more preferably 20-50%.

Also, as required, antioxidants, fillers, cross-linking agents, preservatives or UV absorbers can be used. As antioxidants, tocopherol and its ester derivatives, ascorbic acid, ascorbic acid-stearic acid ester, nordihydroguaretic acid, dibutyl hydroxy toluene (BHT), butyl hydroxy anisole and the like are desirable. As fillers, calcium carbonate, magnesium carbonate, silicate (e.g., aluminum silicate, magnesium silicate, etc.), silicic acid, barium sulfate, calcium sulfate, calcium

zincate, zinc oxide, titanic oxide and the like are desirable. As cross-linking agents, thermosetting resins such as amino resins, phenol resins, epoxy resins, alkyd resins, unsaturated polyesters, etc., isocyanate compounds, block isocyanate compounds, organic type cross-linking agents, and inorganic type cross-linking agents such as metals or metal compounds, are desirable. As preservatives, ethyl p-oxybenzoate, propyl p-oxybenzoate, butyl p-oxybenzoate and the like are desirable. As UV absorbers, p-amino benzoic acid derivatives, anthranilic acid derivatives, salicylic acid derivatives, coumarin derivatives, amino acid type compounds, imidazoline derivatives, pyrimidine derivatives, dioxane derivatives and the like are desirable.

Such antioxidants, fillers, cross-linking agents, preservatives or UV absorbers can be blended in total preferably in an amount of not more than 10% by weight, more preferably not more than 5% by weight and most preferably not more than 2% by weight based on the total weight of the composition in the adhesive layer of the adhesive preparations.

The adhesive layer having such a composition can be prepared by any method. For example, a base composition containing a drug is heat-melted, coated on removable paper or a backing, followed by affixing each to the backing or the removable paper to give the present preparations. Also, base ingredients containing a drug are dissolved in solvent such as toluene, hexane or ethyl acetate, spreaded on removable paper or a backing, dried to remove solvent, followed by affixing to the backing or the removable

paper to give the present preparations.

Further, the adhesive preparations of the invention may take any other structures and materials for each constituent, if the adhesive layer has the above composition containing the organic acid salt and the drug.

For example, in addition to the above adhesive layer the adhesive preparations of the invention can comprise of a backing layer to support it and a removable paper layer set on the adhesive layer.

As to the backing layer, an elastic or a non-elastic backing can be used. For example, it can be selected from fabric, polyurethane, polyester, polyvinyl acetate, polyvinylidene chloride, polyethylene, polyethylene terephthalate, aluminum sheet and the like, or composite materials thereof.

Example

In the following, the invention is explained in more detail by the examples. The invention, however, is not limited to these examples, and various changes may be made without departing from the spirit of the invention. Further, in the examples, all "%"s mean % by weight.

Example 1

Styrene-isoprene-styrene block copolymer (SIS)	24.0%
Alicyclic saturated hydrocarbon (Arkon P-100)	29.5%
Liquid paraffin (Crystol 352)	41.0%
Pyrothiodecane	2.0%
Sodium acetate	1.5%

Ketotifen fumarate	1.5%
Butyl hydroxy toluene [BHT (Yoshinox)]	0.5%
Total amount	100.0%

Sodium acetate (average particle size 7 μm) ground by Jet Mill beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 2

Sodium acetate (average particle size 43 μm) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 1.

Example 3

Sodium acetate (average particle size 91 μm) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 1.

Example 4

SIS	22.5%
Alicyclic saturated hydrocarbon (Arkon P-85)	27.5%
Liquid paraffin	32.0%
Lauryl alcohol	5.0%
Sodium acetate	5.0%
Lidocain hydrochloride	7.5%
BHT	0.5%
Total amount	100.0%

Sodium acetate (average particle size 43 μm) ground using

mortar beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing the removal paper to the backing to give the matrix adhesive preparation of the invention.

Example 5

SIS	15.5%
Polyisobutylene (PIB)	6.5%
Alicyclic saturated hydrocarbon (Arcon P-100)	33.0%
Liquid paraffin	31.5%
Crotamiton	5.0%
Sodium acetate	3.0%
Oxybutynin hydrochloride	5.0%
BHT	0.5%
Total amount	100.0%

Sodium acetate (average particle size 43 μm) ground using a mortar beforehand was used, and the polymer contained was heat-melted. The components were coated on removable paper, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 6

SIS	26.0%
Hydrogenated rosin ester	35.0%
Liquid paraffin	28.6%
Crotamiton	5.0%
Pyrothiodecane	3.0%
Sodium acetate	0.4%

Tizanidine hydrochloride	1.5%
BHT	0.5%
Total amount	100.0%

All the compositions including sodium acetate (average particle size 7 μm) ground by Jet Mill beforehand were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 7

Sodium acetate (average particle size 43 μm) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Example 8

Sodium acetate (average particle size 91 μm) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Example 9

PIB	28.5%
Rosin ester	29.5%
Liquid paraffin	33.5%
l-Menthol	3.0%
Sodium acetate	2.0%
Pridinol mesylate	3.0%
BHT	0.5%
Total amount	100.0%

All the compositions including sodium acetate (average

particle size 7 μm) ground by Jet Mill beforehand was dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 10

SIS	20.5%
PIB	5.5%
Terpene resin (YS resin Px1000)	21.0%
Liquid paraffin	44.0%
Propylene glycol	2.5%
Sodium acetate	3.0%
Tulobuterol hydrochloride	3.0%
BHT	0.5%
Total amount	100.0%

All the compositions including sodium acetate (average particle size 91μm) ground using a mortar beforehand were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 11

SIS	24.0%
Alicyclic saturated hydrocarbon resin (Arcon P-100)	30.0%
Liquid paraffin	38.0%
pyrothiodecane	3.0%
Sodium acetate	1.5%
Fentanyl citrate	3.0%

BHT	0.5%
Total amount	100.0%

Among the above ingredients, all the powder ingredients (sodium acetate, fentanyl citrate) were contained in liquid paraffin, ground by Micros to make the mean diameter 10 μm or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 12

Sodium acetate (average particle size 43 μm) ground using a mortar beforehand was used, and the other ingredients were the same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

Example 13

Sodium acetate (average particle size 91 μm) ground using a mortar beforehand was used, and the other ingredients were same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

Example 14

SIS	21.0%
PIB	9.5%
Aliphatic type hydrocarbon resin (Quintone B170)	25.0%
Polybutene	5.5%
Liquid paraffin	28.5%
Propylene glycol	3.0%

Sodium acetate	2.0%
Propranolol hydrochloride	5.0%
BHT	0.5%
Total amount	100.0%

Among the above ingredients, all the powder ingredients (sodium acetate, propranolol hydrochloride) were contained in liquid paraffin, ground by Micros to make the mean diameter 50 μm or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent, followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 15

SIS	18.0%
PIB	6.0%
Alicyclic saturated hydrocarbon resin (Arkon P-100)	31.5%
Liquid paraffin	30.5%
Lauryl alcohol	5.0%
Sodium acetate	5.0%
Azelastine hydrochloride	3.5%
BHT	0.5%
Total amount	100.0%

Among the above ingredients, all the powder ingredients (sodium acetate, azelastine hydrochloride) were contained in liquid paraffin, ground by Micros to make the mean diameter 100 μm or smaller. This and the other ingredients were dissolved in toluene, coated on removable paper, dried to remove solvent,

followed by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

Example 16

Acrylic polymer (Nissetsu PE-300: Nippon Carbide Industries Co., INC.)	92.0%
Cross-linking agent (Nissetsu CK-100: Nippon Carbide Industries Co., INC.)	0.5%
1-Menthol	3.0%
Sodium acetate	1.5%
Fentanyl citrate	3.0%
Total amount	100.0%

Among the above ingredients, 1-menthol, fentanyl citrate and sodium acetate (average particle size 7 μm) ground by Jet Mill beforehand were added to ethanol, dissolved under stirring at room temperature. The mixture was then added with an ethyl acetate solution of the acrylic polymer and with the cross-linking agent, stirred, coated on removable paper, dried to remove solvent, followed by a heat cross-linking and by affixing said removable paper to the backing to give the matrix adhesive preparation of the invention.

COMPARATIVE EXAMPLE

Comparative example 1

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 1.

Comparative example 2

Sodium acetate (average particle size 535 μm) not yet ground

was used, and the other ingredients and the preparation steps were the same as those of Example 4.

Comparative example 3

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 5.

Comparative example 4

Sodium acetate (average particle size 200 μm) ground using a mortar beforehand was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Comparative example 5

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 6.

Comparative example 6

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 9.

Comparative example 7

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 10.

Comparative example 8

Sodium acetate (average particle size 139 μm) ground using a mortar beforehand was used, and the other ingredients were same as those of Example 11, whereby the preparation was formulated

using a stirrer which has no grinder function.

Comparative example 9

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients were the same as those of Example 11, whereby the preparation was formulated using a stirrer which has no grinder function.

Comparative example 10

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients were the same as those of Example 14, whereby the preparation was formulated out using a stirrer which has no grinder function.

Comparative example 11

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients were the same as those of Example 15, whereby the preparation was formulated using a stirrer which has no grinder function.

Comparative example 12

Sodium acetate (average particle size 535 μm) not yet ground was used, and the other ingredients and the preparation steps were the same as those of Example 16.

(Skin permeability test on hairless mice)

Dorsal skin of a hairless mouse was stripped, and the dermal side was placed to the receptor layer side and installed in a flow-through cell (5 cm^2) around whose periphery warm water at 37°C was circulated. Each of the adhesive preparations obtained in the examples 1-3, 6-8 and 11-13 as well as the comparative

examples 1, 4, 5, 8 and 9 was coated on the stratum corneum side, and sampling was carried out every one hour (or 2 hours) for 12 hours (or 18 hours, 24 hours) at the rate of 5 ml/hour using the physiological saline in the receptor layer. As to the receiver solutions obtained at every hour, the flow amounts were accurately measured, and the drug concentrations were measured by high-performance liquid chromatography, followed by calculation of the permeation rate per hour to determine the skin permeability rate according to the following equation.

Skin permeability rate ($\mu g/cm^2/hr$) =

{sample concentration ($\mu g/ml$) $\times$ flow amount (ml)}/applied area of the preparation (cm^2)

Industrial Applicability

According to the adhesive preparations of the invention, drugs can be efficiently absorbed into circulating blood via skin. Also, side effects of the gastrointestinal system observed in case of oral administration, and side effects in the central nervous system which can occur due to a rapid increase of the blood concentration can be avoided. Further, they are extremely low in irritancy to the skin. Therefore, these are very effective as external preparations aiming at percutaneous application.

Claim

1. An adhesive preparation comprising a base drug salt and an organic acid salt in the form of powder having a mean diameter of 0.1-100 μm.

2. The adhesive preparation according to claim 1, wherein the mean diameter of the organic acid salt is 0.1-10 μm.

3. The adhesive preparation according to claim 1 or 2 comprising the organic acid salt of 0.01-15% by weight.

4. The adhesive preparation according to claim 1 or 2 comprising the base drug salt of 0.1-20% by weight.

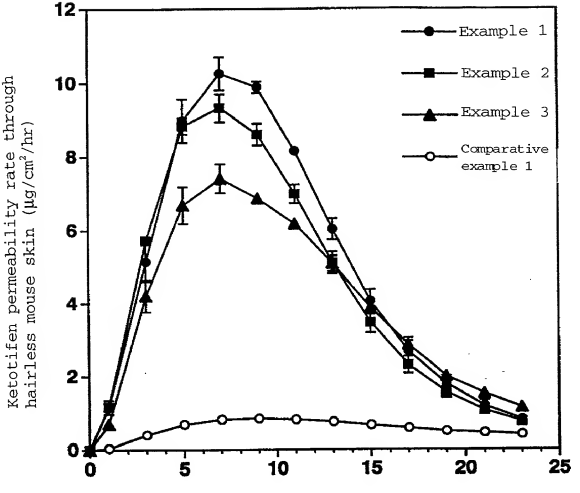
5. The adhesive preparation according to any one of claims 1 to 3, characterized in that the organic acid salt is an acetic acid salt.

6. The adhesive preparation according to claim 5, characterized in that the organic acid salt is sodium acetate.

Abstract

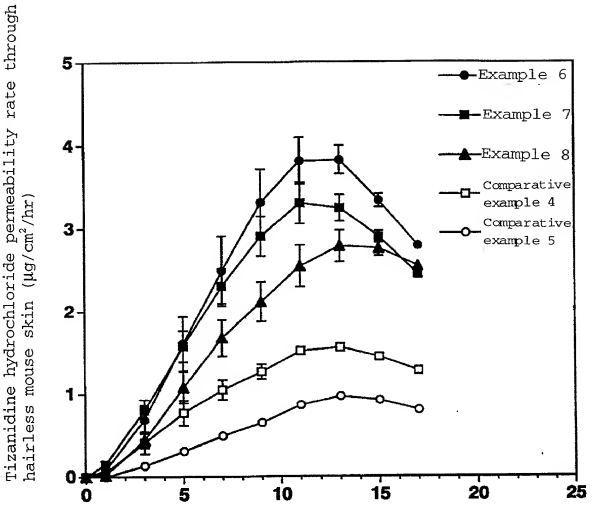
Adhesive preparations with improved percutaneous absorption of physiologically active substances, in particular, matrix adhesive preparations containing a base drug salt and an organic acid salt having an mean diameter of from 0.1 to 100 μm are provided.

Fig. 1



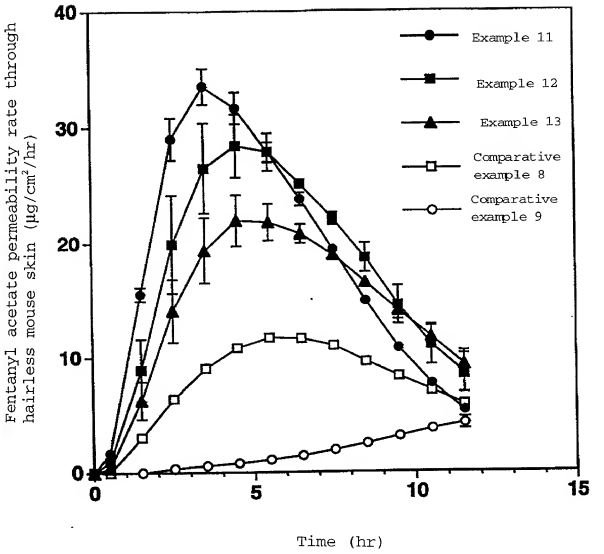
Effects of grinding powder ingredients on permeability of ketotifen formulate through hairless mouse skin

Fig. 2



Effects of grinding powder ingredients on permeability of tizanidine hydrochloride through hairless mouse skin

Fig. 3



Effects of mean diameter on permeability of fentanyl citrate through hairless mouse skin

AP-330/PTPS

Attorney Docket No. **K0448/**

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ADHESIVE PREPARATIONS

the specification of which is attached hereto unless the following is checked:

[X] was filed on April 8, 1999, as PCT International Application No. PCT/JP99/01868, bearing attorney docket No. K0448/.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or section 365(a) of any PCT International application designating at least one country other than the United States listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed:

Prior Foreign PCT International Application(s)and any priority claims under 35 U.S.C. §§119 and 365(a).(b):

			Priority Claimed
10-122758 (Number)	**Japan** (Country-if PCT, so indicate)	**17/04/98** (DD/MM/YY Filed)	**[X]** YES [ ] NO
_____ (Number)	_____ (Country-if PCT, so indicate)	_____ (DD/MM/YY Filed)	[ ] YES [ ] NO
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_____ (Application Number)	_____ (filing date)
_____ (Application Number)	_____ (filing date)

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(Application No.)	(filing date)	(status-patented, pending, abandoned)
(Application No.)	(filing date)	(status-patented, pending, abandoned)

PCT International Applications designating the United States:

(PCT Appl. No.)	(U.S. Ser. No.)	(PCT filing date)	(status-patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Robert M. Abrahamsen	40,886	Jason M. Honeyman	31,624	Stanley Sacks	19,900
John N. Anastasi	37,765	Robert E. Hunt	39,231	Christopher S. Schultz	37,929
Gary S. Engelson	35,128	Ronald J. Kransdorf	20,004	Alan B. Sherr	42,147
Neil P. Ferraro	39,188	Peter C. Lando	34,654	Robert A. Skrivanek, Jr.	41,316
Thomas G. Field	45,596	Helen C. Lockhart	39,248	Paul D. Sorkin	39,039
Stephen R. Finch	42,534	Matthew B. Lowrie	38,228	Alan W. Steele	45,128
Edward R. Gates	31,616	William R. McClellan	29,409	Mark Steinberg	40,828
Richard F. Giunta	36,149	Daniel P. McLoughlin	46,066	Joseph Teja, Jr.	45,157
Peter J. Gordon	35,164	James H. Morris	34,681	John R. Van Amsterdam	40,212
John C. Gorecki	38,471	M. Lawrence Oliverio	30,915	Michael G. Verga	39,410
William G. Gosz	27,787	Timothy J. Oyer	36,628	Robert H. Walat	46,324
Lawrence M. Green	29,384	Edward F. Perlman	28,105	Lisa E. Winsor	44,405
George L. Greenfield	17,756	Michael J. Pomianek	46,190	David Wolf	17,528
James M. Hanifin, Jr.	39,213	Elizabeth R. Plumer	36,637	Douglas R. Wolf	36,971
Therese A. Hendricks	30,389	Randy J. Pritzker	35,986	Ivan D. Zitkovsky	37,482
Steven J. Henry	27,900	Robert E. Rigby, Jr.	36,904		
		Edward J. Russavage	43,069		

Address all telephone calls to John R. Van Amsterdam at telephone no. (617) 720-3500. Address all correspondence to:

John R. Van Amsterdam
c/o Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment,

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Hisakazu Kurita — September 12. 2000

Inventor's signature 1-00 — Date

Full name first or sole inventor: **Hisakazu Kurita**
Citizenship: Japan
Residence: Ibaraki, Japan JP
Post Office Address: c/o HISAMITSU PHARMACEUTICAL CO., INC., Tsukuba Research Laboratories, 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856 JAPAN

Tetsuro Tateishi — September 12. 2000

Inventor's signature 2-00 — Date

Full name second or joint inventor: **Tetsuro Tateishi**
Citizenship: Japan
Residence: Ibaraki, Japan JP
Post Office Address: c/o HISAMITSU PHARMACEUTICAL CO., INC., Tsukuba Research Laboratories, 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856 JAPAN

Hideharu Chono — September 12. 2000

Inventor's signature 3-00 — Date

Full name third or joint inventor: **Hideharu Chono**
Citizenship: Japan
Residence: Ibaraki, Japan JP
Post Office Address: c/o HISAMITSU PHARMACEUTICAL CO., INC., Tsukuba Research Laboratories, 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856 JAPAN

Naruhito Higo — September 12. 2000

Inventor's signature 4-00 — Date

Full name fourth or joint inventor: **Naruhito Higo**
Citizenship: Japan
Residence: Ibaraki, Japan JP
Post Office Address: c/o HISAMITSU PHARMACEUTICAL CO., INC., Tsukuba Research Laboratories, 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856 JAPAN